REMARKS

By the foregoing amendments, claims 99 and 112 have been amended and claim 113 has been added. Support for amended claim 99 can be found in the specification at page 12, second paragraph (optional linker 3); page 15, paragraph 1 and page 16, paragraph 1 (isothiocyanate); paragraph spanning pages 15-16 (functional group converted into R_3); and page 16, paragraph 1 and compounds 36 and 37 on page 18) for amide X group). Support for amended claim 112 can be found in prior claim 70, structure 45. Support for new claim 113 can be found in the subject application at page 12, second paragraph (optional linker 3); page 14, paragraph 1 (DOTA); page 15, paragraph 1 and page 16, paragraph 1 (isothiocyanate); paragraph spanning pages 15-16 (functional group converted into R_3), and page 16, paragraph 1 and compounds 36 and 37 on page 18 for amide X group.

Claims 34, 73, 74 and 99-113 are pending in the application.

The Rejection under 35 USC 112, Second Paragraph

Claim 112 is rejected under Section 112, second paragraph, for failure to complete the Markush group. By the foregoing amendments, claim 112 has been revised to recite a specific compound.

Claim 34 is rejected under Section 112, second paragraph, due to an inconsistency with claim 99 which recites a single molecule. By the foregoing amendments, this inconsistency has been remedied.

Withdrawal of the Section 112 rejections is respectfully requested.

The Rejection under 35 USC 102(b)

Claims 34, 73-74, 99, 100-107, 109-112 are rejected under Section 102(b) as anticipated by Wilbur et al., WO 97/29114. Applicants respectfully traverse this rejection.

Claim 99 recites that linker 1 between the affinity ligand and the X moiety is at least 9 angstroms. While Wilbur et al. may have linkers that are greater than 9 angstroms, it does not recognize the criticality of 9 angstroms as a minimum cut-off value that is necessary to preserve adequate affinity ligand (e.g., biotin) binding to its ligand

(i.e., avidin, streptavidin). This minimal length of 9 angstroms is critical to preservation of an affinity constant the affinity ligand of at least 10^6 M^{-1} to avidin or streptavidin.

Because Wilbur et al. do not teach this minimal linker length as critical to preserve the recited affinity constant to avidin or streptavidin, this reference cannot anticipate claim 99 or any claims dependent thereon. Withdrawal of the Section 102(b) rejection is respectfully requested.

The Rejection under 35 USC 103(a)

Claim 108 stands rejected under Section 103(a) as obvious over Wilbur et al., WO 97/29114 in combination with Rosebrough, S. (1993) J. Pharmacol. Exptl. Therapeut. 265(1):408. Applicants respectfully traverse this rejection.

Wilbur et al. mention many possible "steric moieties" in an alpha position relative to the biotinamide bond. In the paragraph spanning pages 17 and 18 of Wilbur et al., the preferred steric group is a methyl group alpha to the amide bond. While other steric groups are possible, Wilbur et al. state:

> Depending on the steric bulk of the branching group alpha to the amino (or other) functionality attached to the carboxylate, some reduction in binding affinity for biotin-binding proteins may result. The particular application of the biotin compound determines how much steric bulk is desired or can be tolerated in the branched group.

Thus, Wilbur et al. are clear that the steric group at the alpha position may significantly reduce binding affinity of the biotin to avidin or other biotin ligand. Clearly, Wilbur et al. create uncertainty about whether bulky side groups at the alpha position will impact biotin binding to its ligand, and Wilbur et al. make no recommendation whatsoever about side groups at the beta position.

Rosebrough concerns a carboxy group at the alpha position and contains no speculation regarding branching, carboxy or otherwise, at the beta position, and how such substitution might affect biotinidase activity at the amide bond (see Section 132 Declarations of Dr. Sandberg and Dr. Wilbur submitted herewith). However, the Examiner posits that because a carboxy group at the beta position varies by only a methylene group from a carboxy group at the alpha position, the compounds of subject claim 108 containing a beta carboxy are obvious.

Applicants respectfully submit that *prima facie* obviousness has not been established. The Examiner relies on *In re Henze*, 85 USPQ 261 (CCPA 1950), which provides that compounds that differ by a single methylene residue would be expected to have similar properties because they are members of a homologous series. Applicants submit that the rule of *In re Henze* is not applicable here for the following reason.

The subject claim 108 recites an aspartyl residue while Rosebrough describes a cysteinyl residue. Thus, the compound claimed in claim 108 is not a homolog of the Rosebrough compound. In Rosebrough, there is a sulfur atom located beta to the biotinamide bond, whereas in claim 108, the sulfur atom is deleted or replaced by a carboxy or carbonyl group. *In re Henze* does not address sulfur/carboxyl or carbonyl replacements as falling within the definition of "homologues", and the Examiner has cited no evidence that the skilled artisan would recognize compounds that vary by carboxyl or carbonyl replacement of a sulfur atom as part of a homologous series. According to the enclosed Lewis, R. (ed.) Hawley's Condensed Chemical Dictionary (12^{th} ed. 1993), Van Nostrand Reinhold, p. 606, "homologous series" is "a series of organic compounds in which each successive member has one more CH_2 group in its molecule than the preceding member" (see Section 132 Declarations submitted herewith).

Applicants also respectfully submit that *prima facie* obviousness has not been established because there was sufficient unpredictability in the related art of the biotinidase active site and/or binding site, that the skilled artisan could not have reasonably predicted whether the biotin-linker substitutions contemplated in claim 108, i.e., sulfur to carboxyl or carbonyl, and alpha to beta carboxy group, would have disrupted biotinidase cleavage of and/or binding to the biotin amide bond. As attested in the Section 132 Declarations submitted herewith, as of the filing date of the subject application, the skilled artisan could not have conducted reliable modeling of the active site and/or binding site of biotinidase because the X-ray crystalline structure of biotinidase had not yet been obtained, and the mechanism was not known. Thus, without such reliable models, the skilled artisan could not have reasonably predicted whether the modifications contemplated in claim 108 would inhibit biotinidase catalytic and/or binding activity.

Applicants further respectfully submit that *prima facie* obviousness has not been established because all of the elements recited in subject claim 108 are not present in the cited references. Specifically, Rosebrough does not suggest replacement of cysteinyl with aspartyl. While Wilbur et al. may suggest various alpha branches, they do not suggest an aspartyl group or a beta carboxy group. Thus, even if the two references are combined, neither can supply the missing element of an aspartyl group or a beta carboxy group. It is well established that *prima facie* obviousness cannot be established where an element recited in a claim, here, an aspartyl group, is not taught in at least one of the prior art references (*In re Boe & Duke*, 184 USPQ 38, 40 (CCPA 1974)).

At most, the combination of Wilbur et al. and Rosebrough would have made it obvious to try a variety of substitutions on the alpha and beta carbons, and/or to substitute the sulfur of the DACB compound of Rosebrough with a carboxy or carbonyl group. However, "obvious to try" is not the proper standard in establishing *prima facie* obviousness (*In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988)).

In view of the foregoing arguments, Applicants respectfully request withdrawal of the Section 103 rejection.

Closing Remarks

It is believed that the foregoing remarks and amendments bring the subject application into condition for allowance and notification of same is earnestly requested. If the Examiner believes a phone conference would expedite prosecution, he is invited to phone the undersigned at 303-268-0066.

Submitted herewith is Petition for Extension of Time for 3 months and a check for $535 to cover the extension fee and new claims fee (small entity). It is believed that no other fees are due with this submission. If this is in error, please charge any necessary fees to Deposit Account No. 19-5117.

Respectfully submitted,

Margaret M. Wall

Sept 13, 2006
Date

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